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APPLICANT: SAMUEL C. WADSWORTH ET AL
TITLE: METHODS OF TREATING DIABETES AND OTHER BLOOD
SUGAR DISORDERS
ATTORNEY/AGENT: JENNIFER D. TOUSIGNANT
REG. NO. 54,498
DOCKET NO.: 5062CIP

TELEPHONE: (508) 270-2499
SHEET 1 OF 36

SEAP.GLP-1Gly8

10 20 30 40 50

GAATTCCGCCACCATGCTGCTGCTGCTGCTGGGCTGCGCCTG
CTTAAGGCGGGTGGTACGACGACGACGACGACGACCCGGACGCGGAC

M L L L L L L L G L R L>

SEAP SIGNAL PEPTIDE >

60 70 80 90 100

CAGCTGAGCCTGGGCCACGGCGAGGGCACCTCACCAAGCGACGTGAGCAG
GTCGACTCGGACCCGGTGCCGCTCCGTGGAAGTGGTCGCTGCACTCGTC

Q L S L G>

SEAP SIG > H G E G T F T S D V S S
GLP-1GLY8 >

110 120 130 140 150

CTACCTGGAGGGCCAGGCCAAGGAGTTATCGCTGGCTGGTGAAGG
GATGGACCTCCGGTCCGGCGTTCTCAAGTAGCGGACCGACCACCTCC

Y L E G Q A A K E F I A W L V K>

GLP-1GLY8 >

GGCGCGGC

GGCGCCG

G R G>

>

Figure 1

Exendin-4, GLP-1Gly8

10 20 30 40 50
GAATTCCGCCACCATGAAGATCATCCTGTGGCTGTGTGTTGGCCTG
CTTAAGGCGGGTGGTACTTCTAGTAGGACACCGACACACACAAGCCGGAC
M K I I L W L C V F G L>
PROEXENDIN >

60 70 80 90 100
TTCCTGGCCACCCCTGTTCCCCATCAGCTGGCAGATGCCCGTGGAGTCCGG
AAGGACCGGTGGACAAGGGTAGTCGACCGTCTACGGCACCTCAGGCC
F L A T L F P I S W Q M P V E S G>
PROEXENDIN >

110 120 130 140 150
CCTGTCCCTCCGAGGACTCCGCCAGCTCCGAGAGCTTCGCCAAGCGCATCA
GGACAGGAGGCTCCTGAGGCCGTCGAGGCTCTCGAAGCGGTTCGCGTAGT
L S S E D S A S S E S F A K R I>
PROEXENDIN >

160 170 180 190 200
AGCGCCACGGCGAGGGCACCTCACCGAGCGACGTGAGCAGCTACCTGGAG
TCGCAGGTGCCGCTCCGTGGAAGTGGTCGCTGCACTCGTCATGGACCTC
H G E G T F T S D V S S Y L E>
GLP-1 GLY-8 >

K R>
>

210 220 230 240 250
GGCCAGGCCGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCCGGCTG
CCGGTCCGGCGGTTCTCAAGTAGCGGACCGACCACCTCCGGCGCCGAC
G Q A A K E F I A W L V K G R G>
GLP-1 GLY-8 >

Figure 2

Helodermin.GLP-1Gly8

10 20 30 40 50
GAATTCCGCCACCATGAAGAGGCATCCTGTGGCTGTGTGTTGGCCTG
CTTAAGGCAGGGTGGTACTTCTCGTAGGACACGACACACAAACCGGAC
M K S I L W L C V F G L>
PRO-HELODERMIN >

60 70 80 90 100
*
CTGATTGCCACCCCTGTTCCCTGTGAGCTGGCAGATGCCATCAAGAGCAG
GACTAACGGTGGGACAAGGGACACTCGACCGTCTACCGGTAGTTCTCGTC
L I A T L F P V S W Q M A I K S R>
PRO-HELODERMIN >

110 120 130 140 150
ACTGT CCT CTGAGGA CTCTGAGACAGACCA GAGACTGAAGCGCATCAAGC
TGACAGGAGACTCCTGAGACTCTGTCTGGTCTCTGACTTCGCGTAGTTCG
L S S E D S E T D Q R L K R I K>
PRO-HELODERMIN >

160 170 180 190 200
*
GCCACGGCGAGGGCACCTCACCA CGACGTGAGCAGCTACCTGGAGGGC
CGGTGCCGCTCCCGTGGAAAGTGGTCGCTGCACTCGTCGATGGACCTCCCG
R>
H G E G T F T S D V S S Y L E G>
PRODUCT=GLP-1 >

210 220 230 240
CAGGCCGCCAAGGAGTTCATGCCCTGGCTGGTGAAGGGCCCGCGC
GTCCGGCGGTTCCCTCAAGTAGCGGACCGACCACTTCCC GGCGCCG
Q A A K E F I A W L V K G R G>
PRODUCT=GLP-1 >

Figure 3

GIP.GLP-1GLy8

10 20 30 40 50
GAATTCCGCCACCATGGTGGCCACCAAGACCTTGCCCTGCTGCTCCTG
CTTAAGGCGGGTGGTACCAACCGGTGGTCTGGAACGGACGACGAGGAC
M V A T K T F A L L L L >
PRO-GIP >

60 70 80 90 100
*
AGCCTCTCCTGGCTGTGGACTGGCGAGAAGAAGGAAGGCCACTTCAG
TCGGAGAAGGACCGACACCCCTGACCCGCTCTTCTCCTCCGGTGAAGTC
S L F L A V G L G E K K E G H F S >
PRO-GIP >

110 120 130 140 150
CGCCCTGCCAGCCTGCCAGTGGCAGCCATGCCAAGGTGAGCTCCCCAC
GCGGGACGGGTCGGACGGTCACCCGTCGGTACGGTTCCACTCGAGGGGTG
A L P S L P V G S H A K V S S P >
PRO-GIP >

160 170 180 190 200
*
AGAACGGCATCAAGGCCACGGCGAGGGCACCTTACCCAGCGACGTGAGC
TCTTCGCGTAGTTCGCGGTGCCGCTCCGTGGAAGTGGTCGCTGCACTCG
Q K R I K R >
PRO-GIP > H G E G T F T S D V S >
GLP-1GLY8 >

210 220 230 240 250
AGCTACCTGGAGGGCCAGGCCAGGCCAAGGAGTTCATCGCCTGGCTGGTGAA
TCGATGGACCTCCGGTCCGGCGGTTCCCTCAAGTAGCGGACCGACCACTT
S Y L E G Q A A K E F I A W L V K >
GLP-1GLY8 >

260
GGGCCGGCG
CCCGGGCGCCG
G R G >
>

Figure 4

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TELEPHONE: (508) 270-2499
 SHEET 5 OF 36

IGF-I (furin) . GLP-1Gly8

10 20 30 40 50
 GAATTCCGCCCACCATGGGCAAGATCAGCAGCCTGCCACCCAGCTGTC
 CTTAAGGCGGGTGGTACCCGTTCTAGTCGTCGGACGGGTGGTCGACAAG

M G K I S S L P T Q L F>
 _____ IGF1 1-48 _____>

60 70 80 90 100

*

AAGTGCTGCTTTGTGACTTCCTGAAGGTGAAGATGCACACCATGAGCTC
 TTCACGACGAAAACACTGAAGGACTTCCACTTCTACGTGTGGTACTCGAG
 K C C F C D F L K V K M H T M S S>
 _____ IGF1 1-48 _____>

110 120 130 140 150

CAGCCACCTGTTCTACCTGGCCCTGTGCCTGCTGACCTCACAGCTCCG
 GTCGGTGGACAAGATGGACCGGGACACGGACGACTGGAAGTGGTCGAGGC
 S H L F Y L A L C L L T F T S S>
 _____ IGF1 1-48 _____>

160 170 180 190 200

*

CCACAGCCAAGCGCATCAAGGCCACGGCGAGGGCACCTCACAGCGAC
 GGTGCGGTTCGCGTAGTCGCGGTGCCGCTCCGTGGAAGTGGTCGCTG
 A T A>

>K R I K R>

_____ FURIN CL _____>H G E G T F T S D>
 _____ PRODUCT=GLP-1 _____>

210 220 230 240 250

GTGAGCAGCTACCTGGAGGGCCAGGCCAAGGAGTTCATGCCCTGGCT
 CACTCGTCGATGGACCTCCGGTCCGGCGGTTCTCAAGTAGCGGACCGA
 V S S Y L E G Q A A K E F I A W L>
 _____ PRODUCT=GLP-1 _____>

260

GGTGAAGGGCCGCGGC
 CCACTTCCCAGGCGCCG
 V K G R G>
 _____ PRODUCT= _____>

Figure 5

IGF-I.GLP-1Gly8

10 20 30 40 50 **new case acceptance**

GAATTCCGCCACCATGGGCAAGATCAGCAGCCTGCCACCCAGCTGTC
CTTAAGGCGGGTGGTACCCGTTCTAGTCGTCGGACGGGTGGTCCGACAAG

M G K I S S L P T Q E F V
IGF-I SIGNAL PEPTIDE

60 70 80 90 100

AAGTGCTGCTTTGTGACTTCCTGAAGGTGAAGATGCACACCATGAGCTC

TTCACGACGAAACACTGAAGGACTTCCACTTCTACGTGTGGTACTCGAG
K C C F C D F L K V K M H T M S S >
IGF-I SIGNAL PEPTIDE >

IGF-I SIGNAL PEPTIDE >

110 120 130 140 150

CAGCCACCTGTTCTACCTGGCCCTGTGCCTGCTGACCTTCACCAGCTCCGGTCGGTGGACAAGATGGACCGGGACACGGACGACTGGAAGTGGTCGAGGC

S H L F Y L A L C L L T F T S S>
IGF-I SIGNAL PEPTIDE >

160 170 180 190 200

六

CCACAGCCCACGGCGAGGGCACCTCACCGCAGCGACGTGAGCAGCTACCTG
GGTGTGGGTGCCGCTCCCGTGGAAAGTGGTCGCTGCACTCGTCGATGGAC
A T A>

...>H G E G T F T S D V S S Y L>
GLP-1GLY8>

210 220 230 240 250
 GAGGGCCAGGCCAAGGAGTTCATCGCCTGGCTGGTGAAGGGCCGCGC
 CTCCCGGTCCGGCGTTCTCAAGTAGCGGACCGACCACTCCGGCGCCG
 E G Q A A K E F I A W L V K G R G>
 GLP-1GLY8

Figure 6

Preproglucagon.GLP-1Gly8

10	20	30	40	50	
GAATTCCGCCACCATGAAAAGCATTACTTGTGGCTGGCTGTTGTG					
CTTAAGGCGGGTGGTACTTTCGTAAATGAAACACCGACCCGACAAACAC					
	M K S I Y F V A G L F V >				
	GLUCAGON SIGNAL PEPTIDE				

110	120	130	140	150											
CGTGAGCAGCTACCTGGAGGGCCAGGCCAAGGAGTTCATCGCCTGGC															
GCACTCGTCGATGGACCTCCGGTCCGGCGGTTCTCAAGTAGCGGACCG															
V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W>
<hr/>															
GLP-1GLY8															

160

ACCACTTCCCCGGCGCGCG
L V K G R G>
____ GLP-1GLY8 ____ :

Figure 7

Alpha-1 antitrypsin.GLP-1Gly8

10	20	30	40	50								
GAATTCCGCCACCATGCCCTCTCTGTCTCCTGGGGCATCCTCCTGCTG												
CTTAAGGCGGGTGGTACGGGAGAAGACAGAGGACCCGTAGGAGGACGAC												
	M	P	S	S	V	S	W	G	I	L	L	L>
	A1AT SIGNAL PEPTIDE											

60 70 80 90 100
 *
 GCAGGCCCTGTGCTGCCTGGTCCCTGTCTCCCTGGCTCACGGCGAGGGCAC
 CGTCCGGACACGACGGACCAGGGACAGAGGGACCGAGTGGCTCCGTG
 A G L C C L V P V S L A>
A1AT SIGNAL PEPTIDE >H G E G T>

	110	120	130	140	150
CTTCACCAGCAGCTGAGCAGCTACCTGGAGGGCCAGGCCGCCAAGGGAGT					
GAAGTGGTCGCTGCACTCGTCGATGGACCTCCGGTCCGGCGGTTCCCTCA					
F T S D V S S Y L E G Q A A K E >					
GLP-1GLY8					

160	170
TCATCGCCTGGCTGGTGAAGGGCCGCGGC	
AGTAGCGGACCGACCACCTTCCCGGCGCCG	
F . I A . W L V K G R G >	
GLP-1 GLY8 >	

Figure 8

Factor IX.GLP-1Gly8

10 20 30 40 50
GAATTCCGCCACCATGCAGAGAGTGAACATGATCATGGCAGAAATCCCCA
CTTAAGGCGGGTGGTACGTCTCTACTTGTACTAGTACCGTCTTAGGGGT

M Q R V N M I M A E S P >
PRO-FIX

60 70 80 90 100

GGCCTGATCACCATCTGCCTGGGATACCTCCTGTCTGCTGAGTGCAC
CCGGACTAGTGGTAGACGGAGGACCCATGGAGGACAGACGACTCACGTC

HISTORICAL PERSPECTIVE ON THE DEVELOPMENT OF THE POLYMER INDUSTRY

PRO-FIX

110 120 130 140 150
AGTGTTCCTGGACCATGAGAAATGCCAACAGATTCTGAACAGACCCAAAGA

TCACAAGGACCTGGTACTCTTACGGTTCTAAGACTTGTCTGGGTTCT
V F L D H E N A N K I L N R P K>
PRO-FIX

160 170 180 190 200

```
GGCATGGGGAGGGCACCTCACCGAGCGACGTGAGCAGCTACCTGGAGGGC  
CCGTACCCCTCCCGTGGAAAGTGGTCGCTGCACTCGTCGATGGACCTCCCG  
R>
```

F T S D
GLP-1 GLY-8

210	220	230	240
CAGGCCGCGCAAGGAGTCATCGCTGGCTGGTGAAGGGCCGCGC	GTCCGGCGGTTCTCAAGTAGCGGACCGACCACTTCCCGGCGCG		
Q A A K E F I A W L V K G R G>			

Figure 9

Exendin-4 (IGF-I).GLP-1GLY8

10 20 30 40 50

GAATTCCGCCACCATGAAGATCATCCTGTGGCTGTGTGTTGGCCTG
 CTTAAGCGGGTGGTACTTCTAGTAGGACACCGACACACACAAGCCGGAC

M K I I L W L C V F G L>

PRO-EXENDIN-4 >

60 70 80 90 100

*

TTCCCTGGCCACCCCTGTTCCCCATCAGCTGGCAGATGCCGTGGAGTCCGG
 AAGGACCGGTGGACAAGGGTAGTCGACCGTCTACGGCACCTCAGGCC

F L A T L F P I S W Q M P V E S G>

PRO-EXENDIN-4 >

110 120 130 140 150

CCTGTCCTCCGAGGACTCCGCCAGCTCCGAGAGGCCCTCTGAAGCCTGCCA
 GGACAGGAGGCTCCTGAGGCGGTGAGGCTCTCGGGAGACTTCGGACGGT

L S S E D S A S S E S>

PRO-EXENDIN-4 >P L K P A>

IGF-I PRO >

160 170 180 190 200

*

AGTCTGCCAGACATGGAGAGGGCACCTCACATCTGACGTGAGCAGCTAC
 TCAGACGGTCTGTACCTCTCCGTGGAAGTGTAGACTGCACTCGTCGATG

H G E G T F T S D V S S Y>

GLP-1GLY8 >

K S A R>

>

210 220 230 240 250

CTGGAGGGCCAGGCCGCCAAGGAGTTCATGCCCTGGCTGGTGAAGGGCCGGCG
 GACCTCCCGGTCCGGCGGTTCCCTCAAGTAGCGGACCGACCACTTCCGGCGCCG

L E G Q A A K E F I A W L V K G R G>

GLP-1GLY8 >

Figure 10

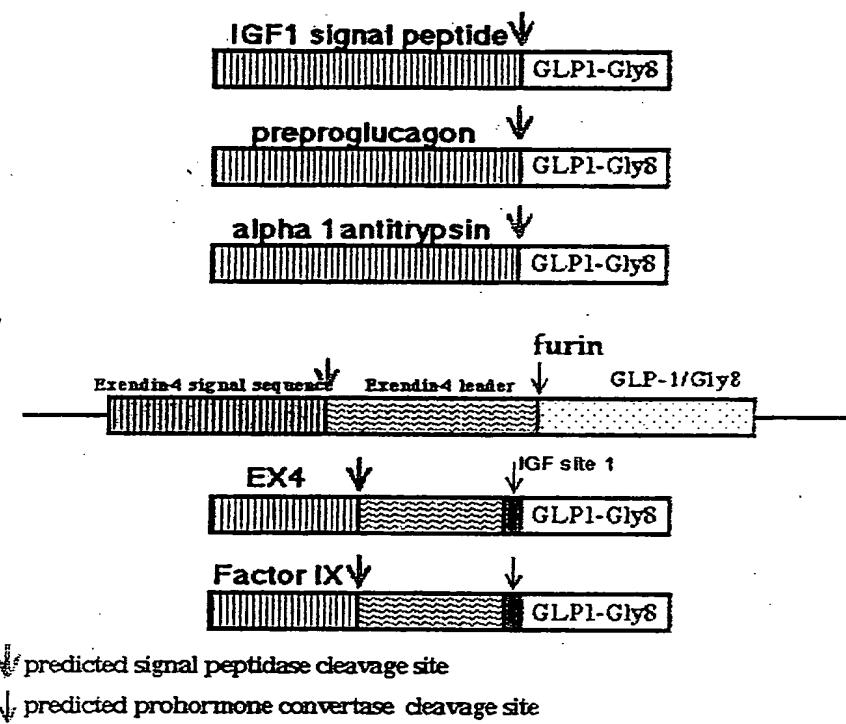


Figure 11

GLP-1 Expression Levels in the Supernatant of Transfected 293 Cells

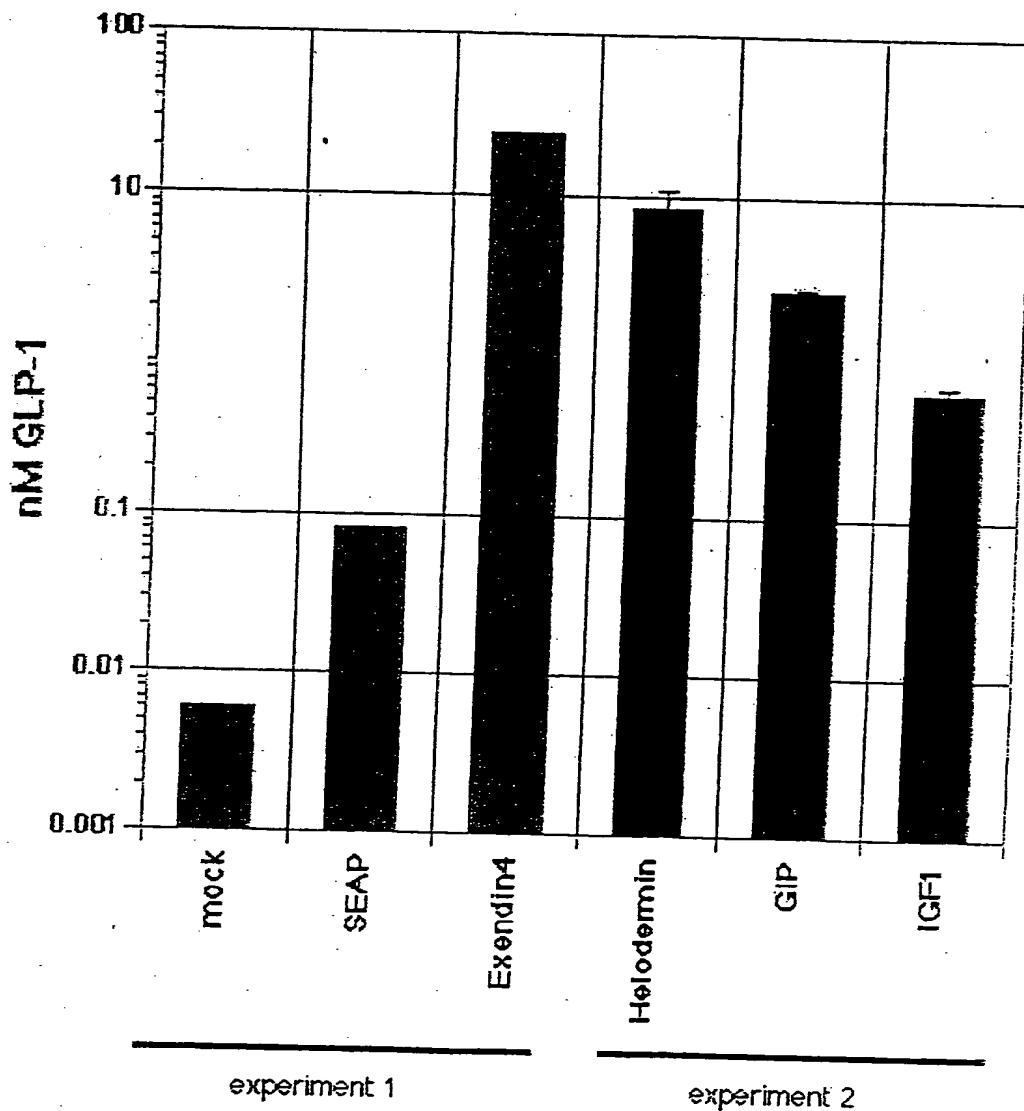


Figure 12

[GLP-1] in Transfected 293 Supernatants

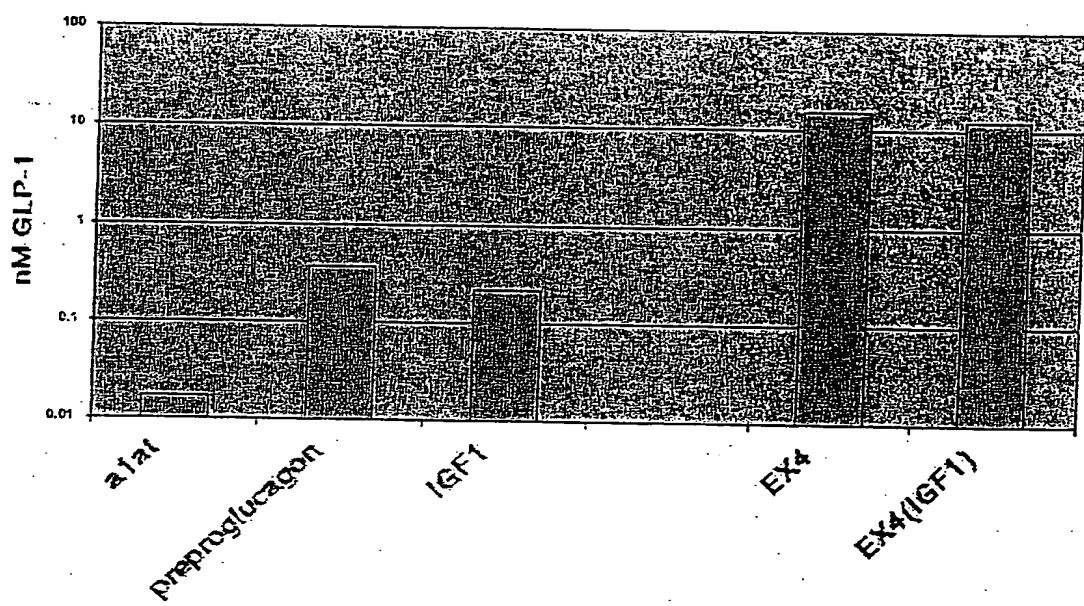


Figure 13

GLP-1 Secreted From C2C12 Cells

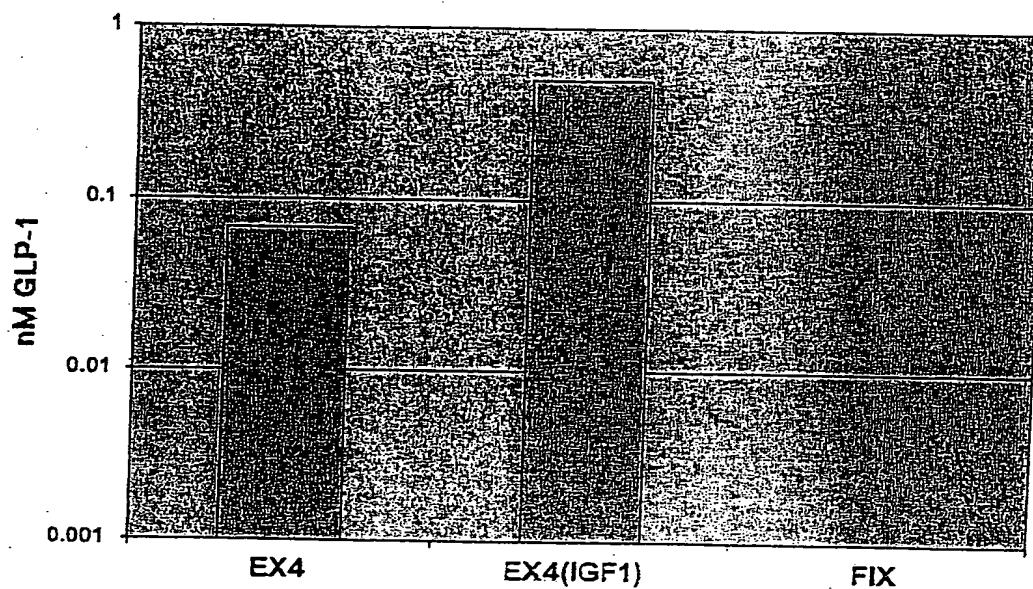


Figure 14

GLP1 Concentration in Plasma

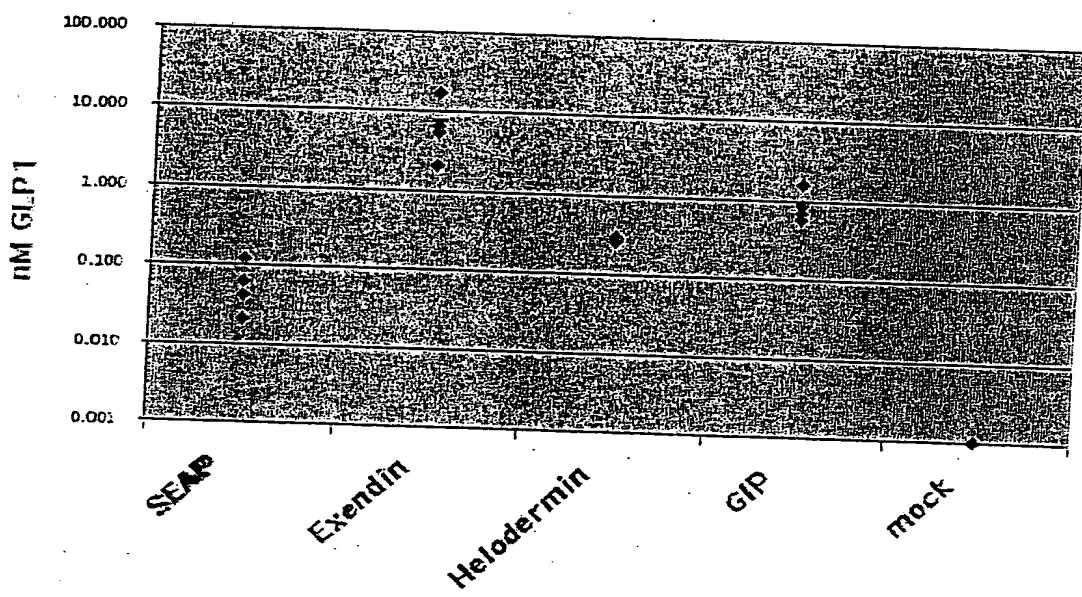


Figure 15

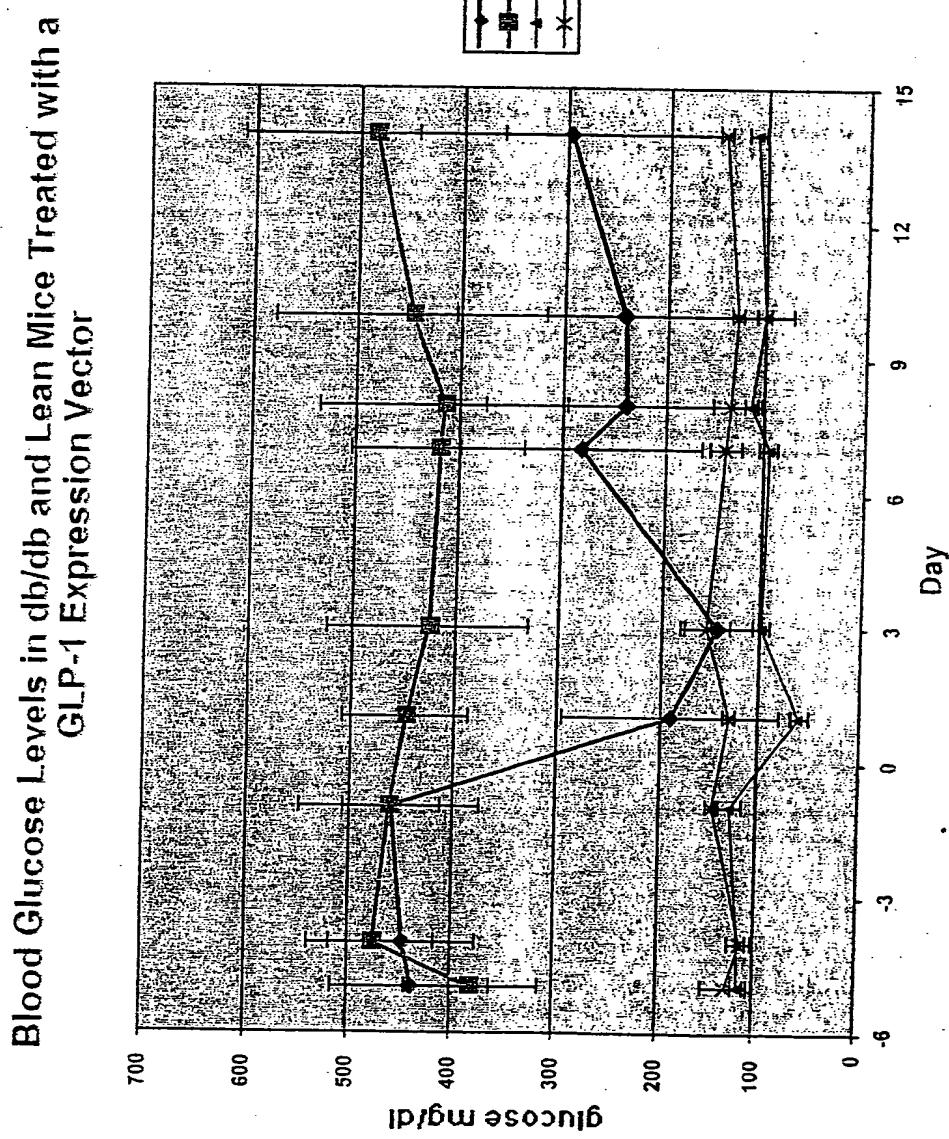


Figure 16

APPLICANT: SAMUEL C. WADSWORTH ET AL.
TITLE: METHODS OF TREATING DIABETES AND OTHER BLOOD
SUGAR DISORDERS
ATTORNEY/AGENT: JENNIFER D. TOUSIGNANT
REG. NO. 54,498 **TELEPHONE: (508) 270-2499**
DOCKET NO.: 5062CIP **SHEET 17 OF 36**

GeneSwitch Control of GLP-1 Expression

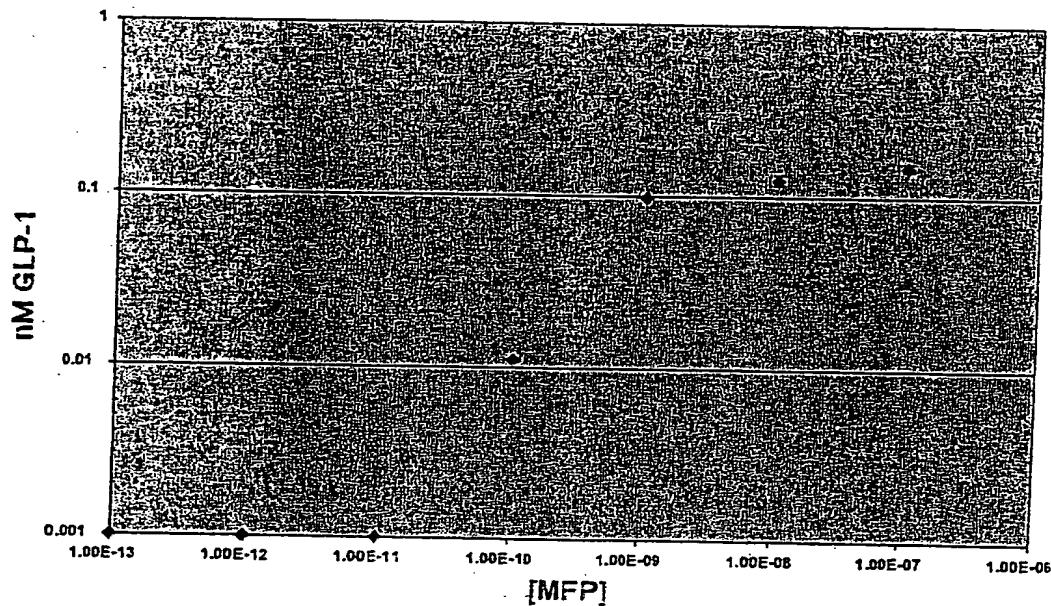


Figure 17

Examples of Modified GLP-1

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys (SEQ ID NO:23)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵ (SEQ ID NO: 24)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg (SEQ ID NO:25)

His⁷-Val-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:26)

His⁷-Ala-Gln-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:27)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Thr-Ser-Lys-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷ (SEQ ID NO:28)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Lys-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:29)

His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-D-GLn³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:30)

Figure 18A

Asp-Glu-Phe-Glu-Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:31)

Glu-Phe-Glu-Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:32)

Arg-His⁷-Ala-Glu-Gly¹⁰-Thr-Phe-Thr-Ser-Asp¹⁵-Val-Ser-Ser-Tyr-Leu²⁰-Glu-Gly-Gln-Ala-Ala²⁵-Lys-Glu-Phe-Ile-Ala³⁰-Trp-Leu-Val-Lys-Gly³⁵-Arg-Gly³⁷-COOH (SEQ ID NO:33)

Figure 18B

Figure 19

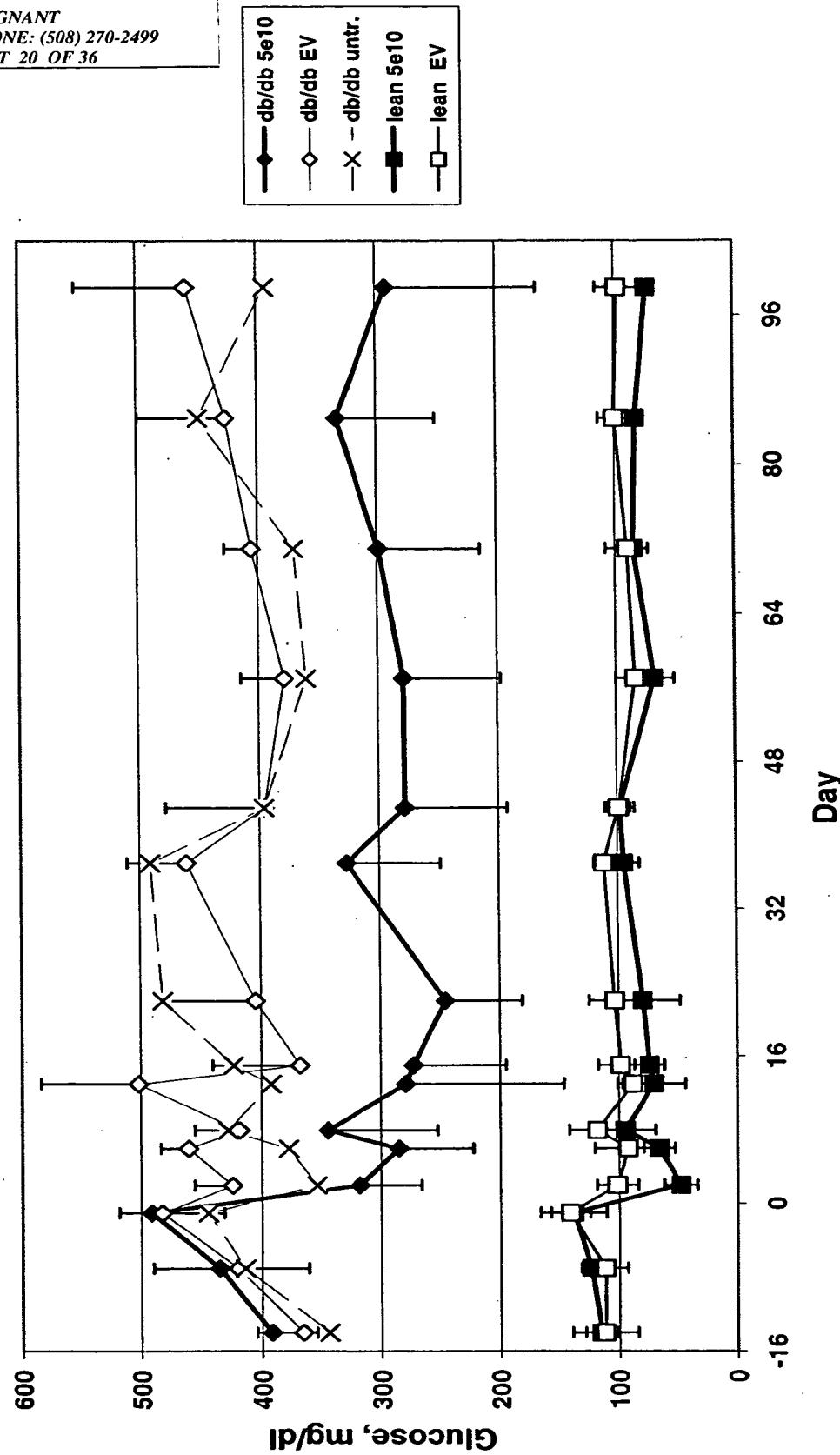


Figure 20

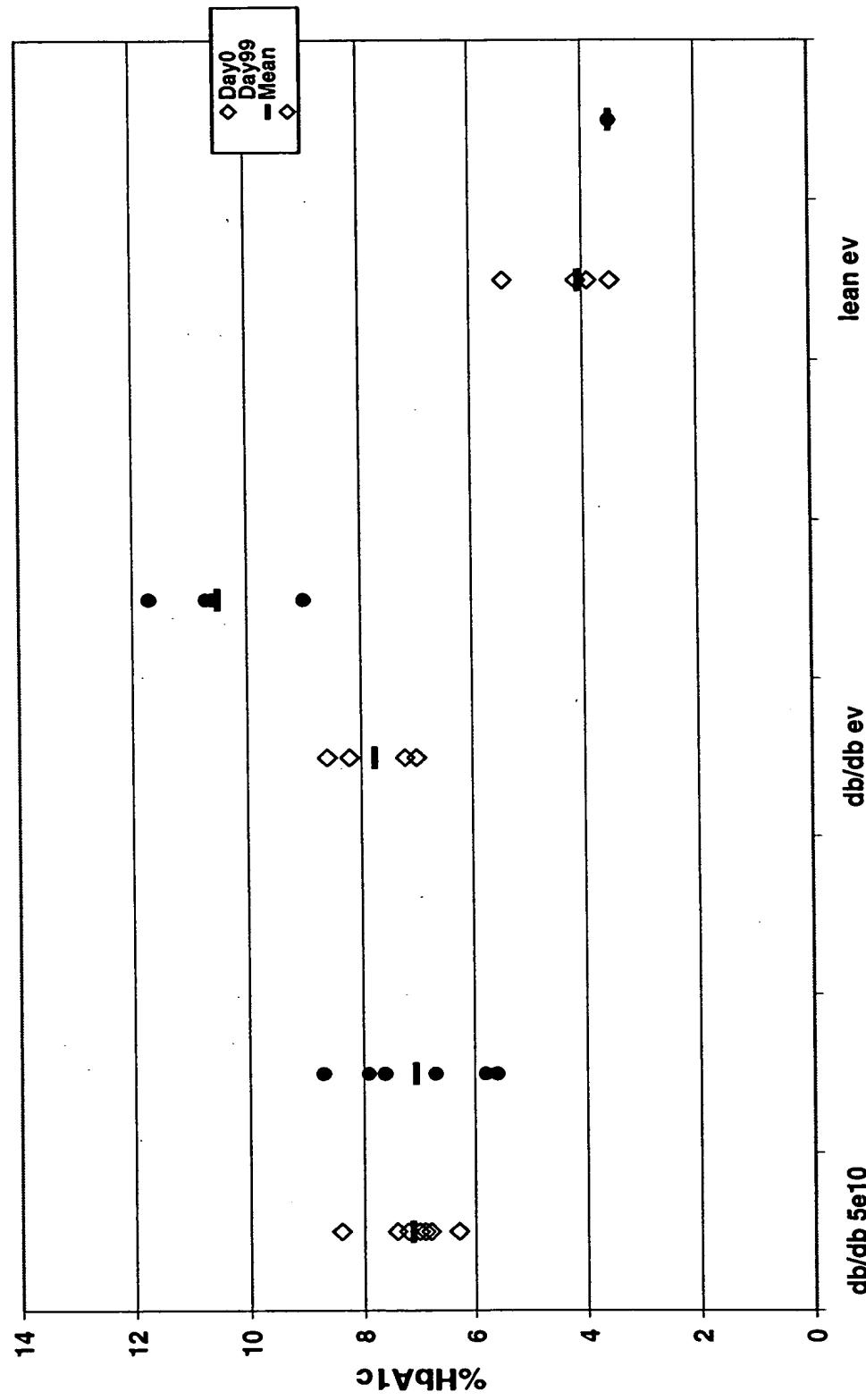


Figure 21

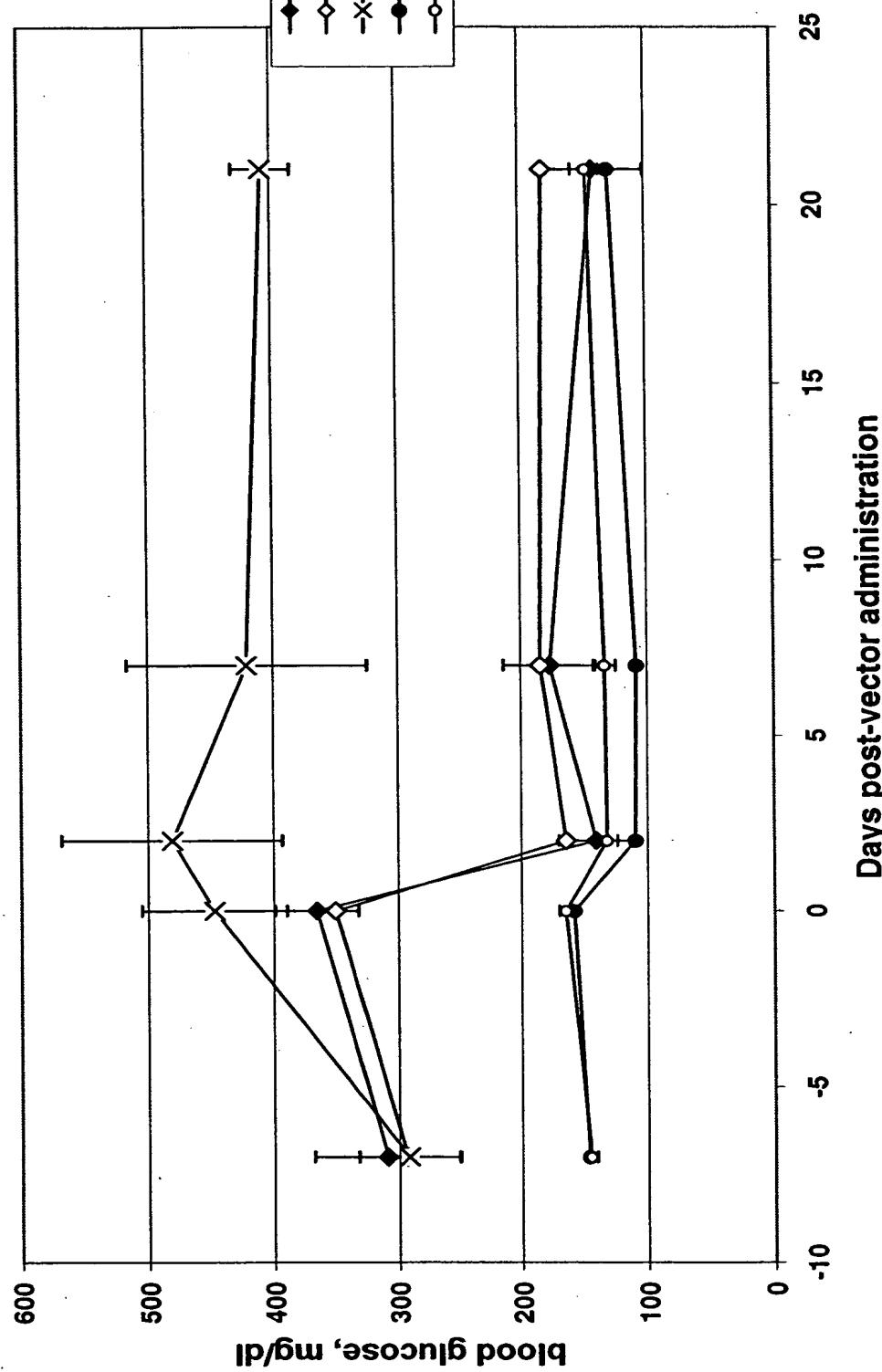


Figure 22

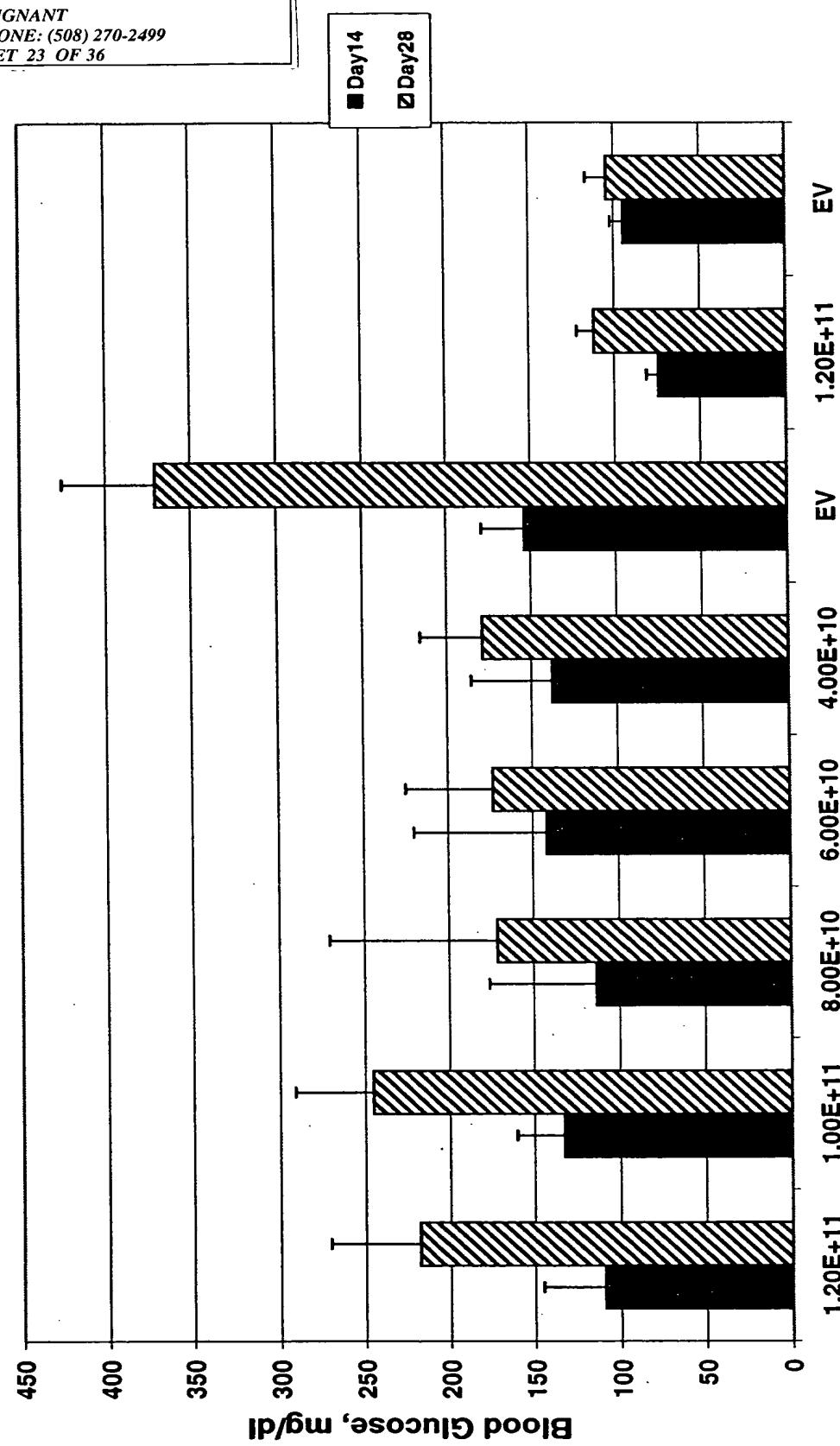


Figure 23

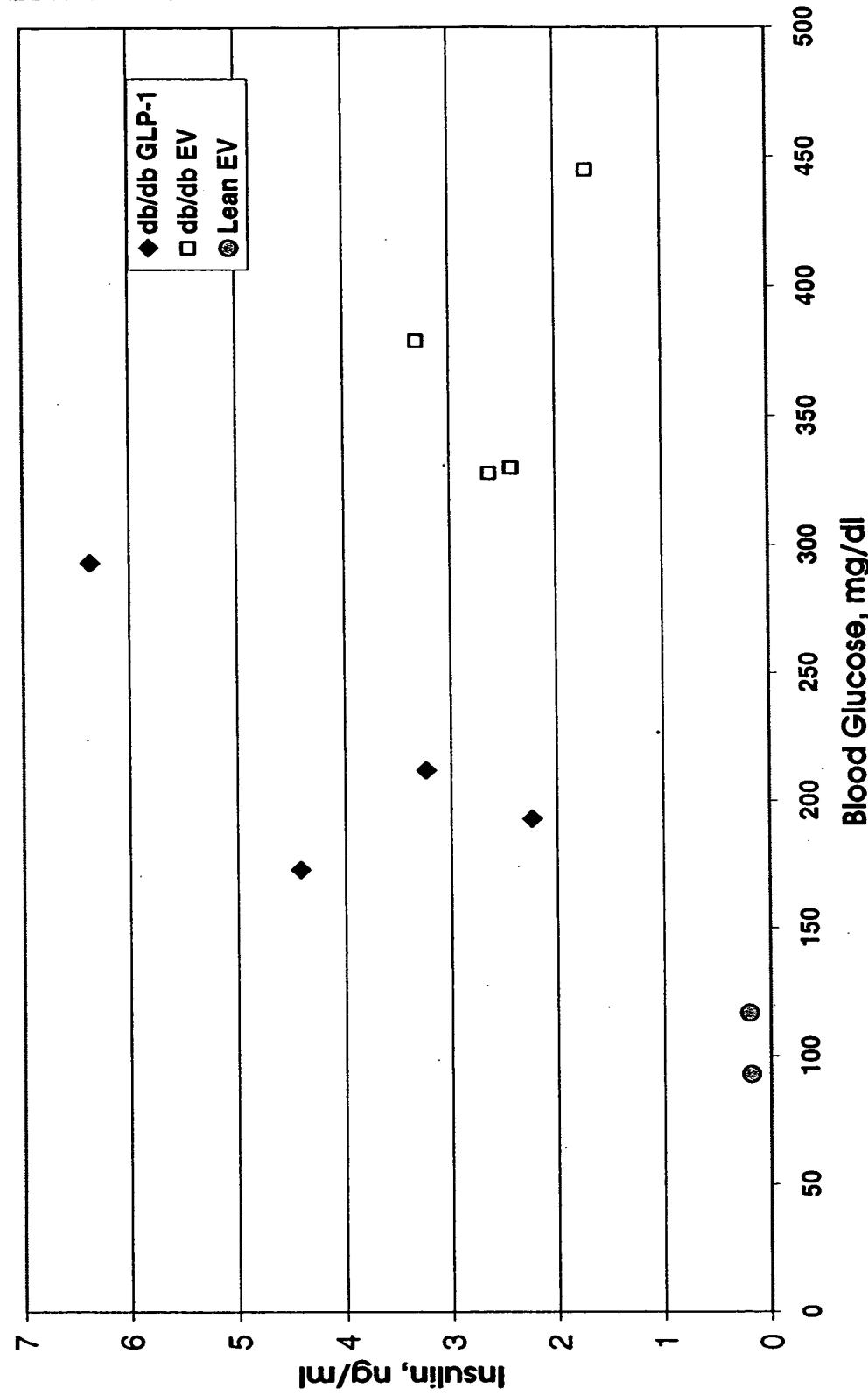


Figure 24

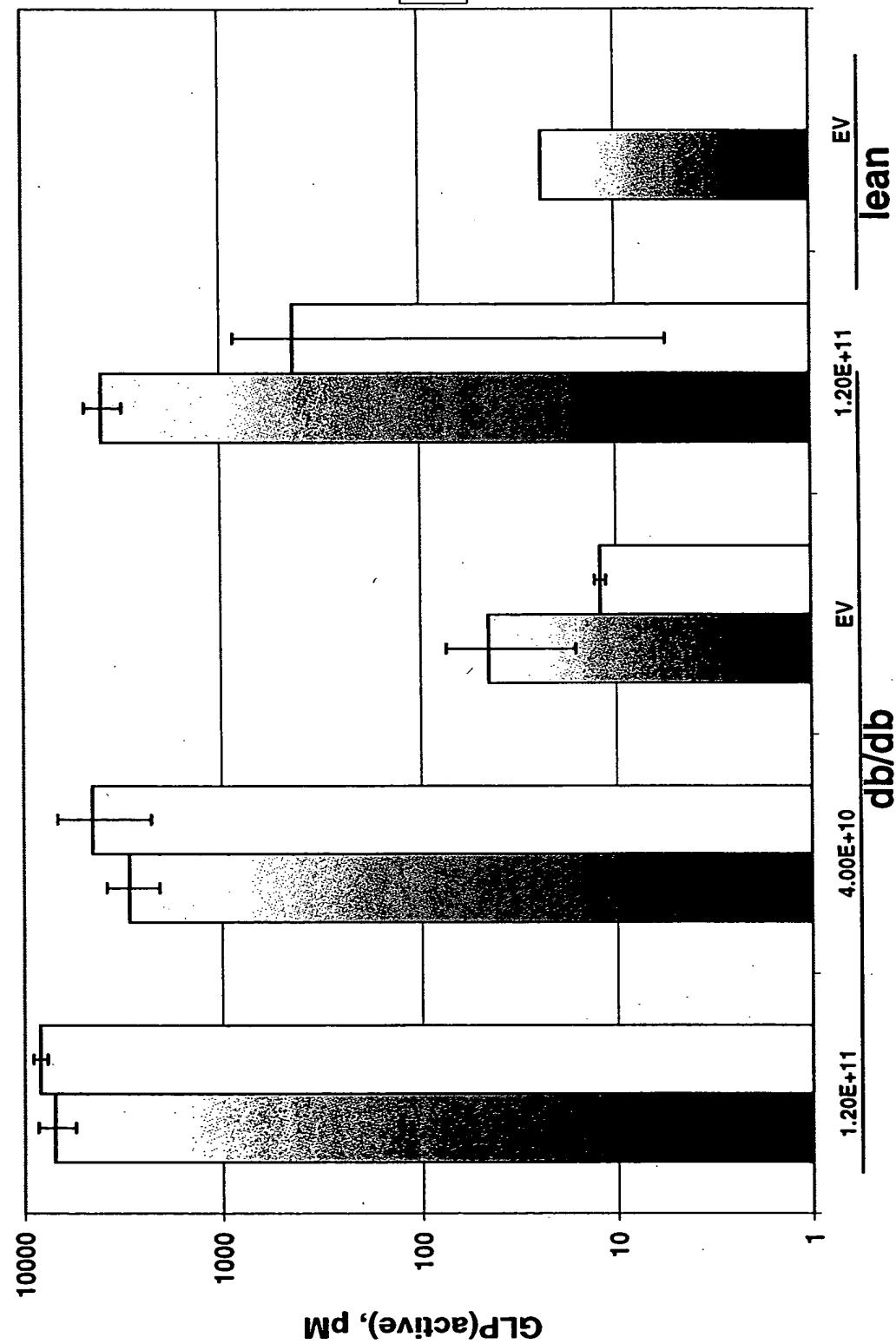


Figure 25

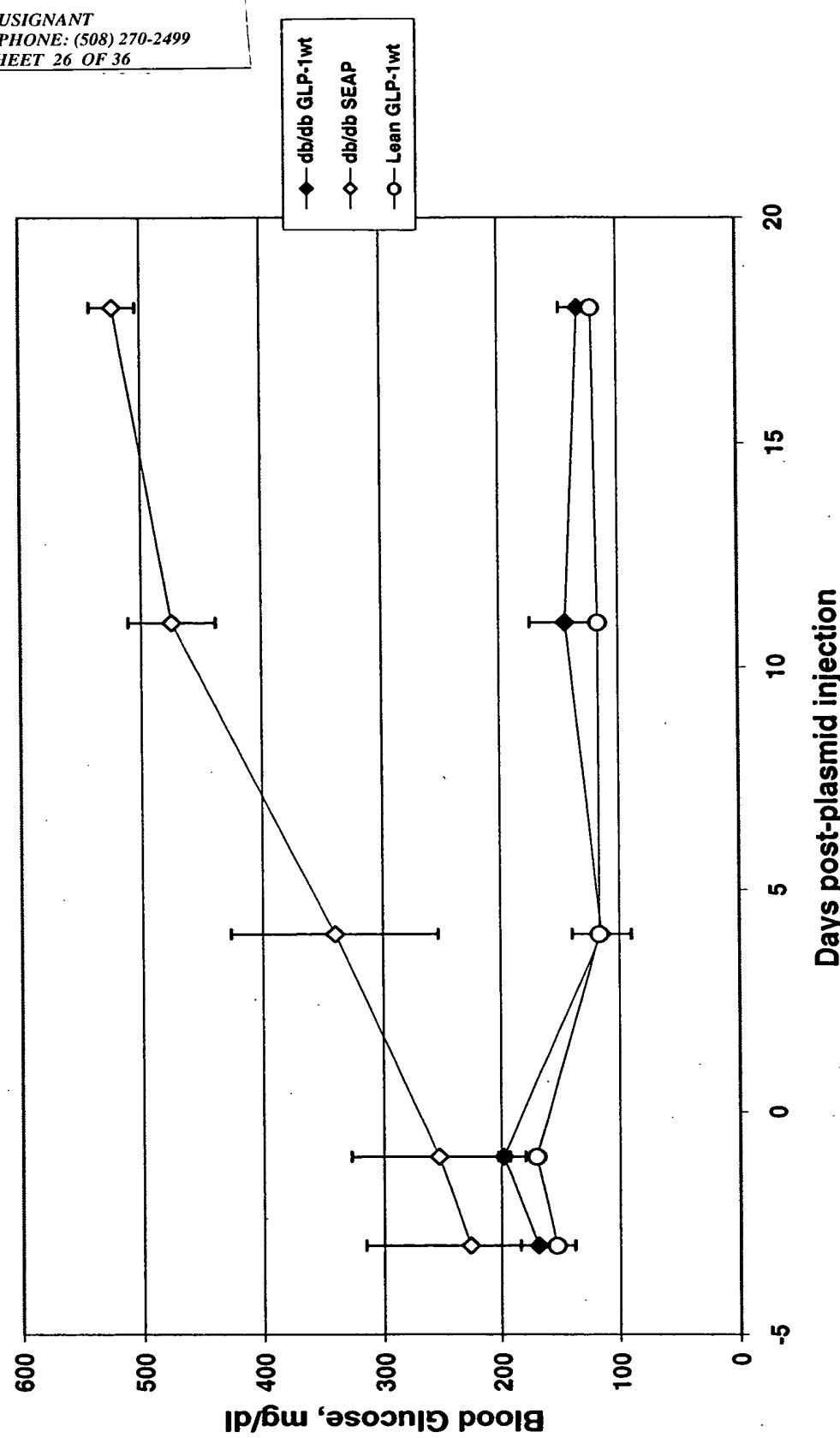


Figure 26

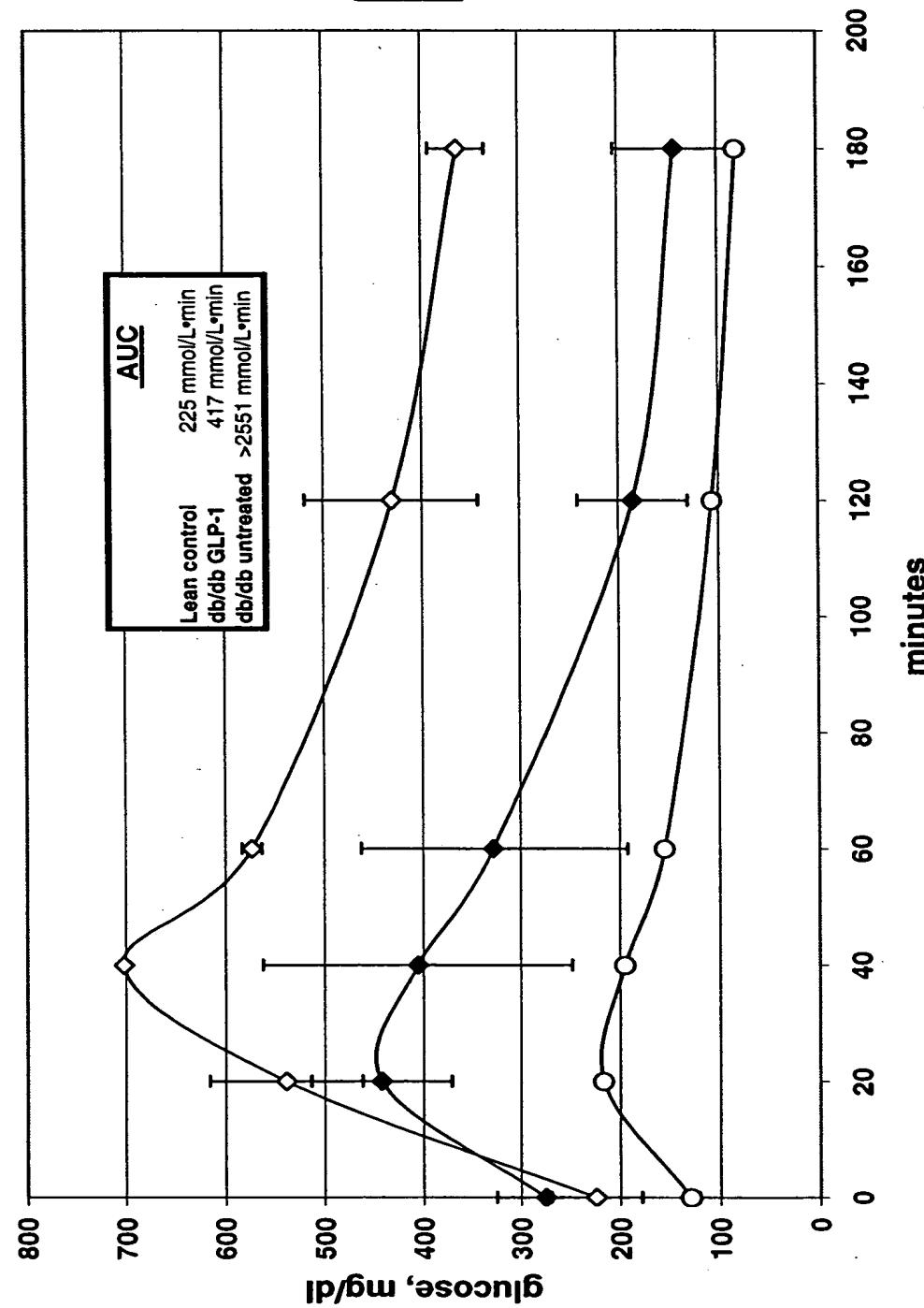


Figure 27

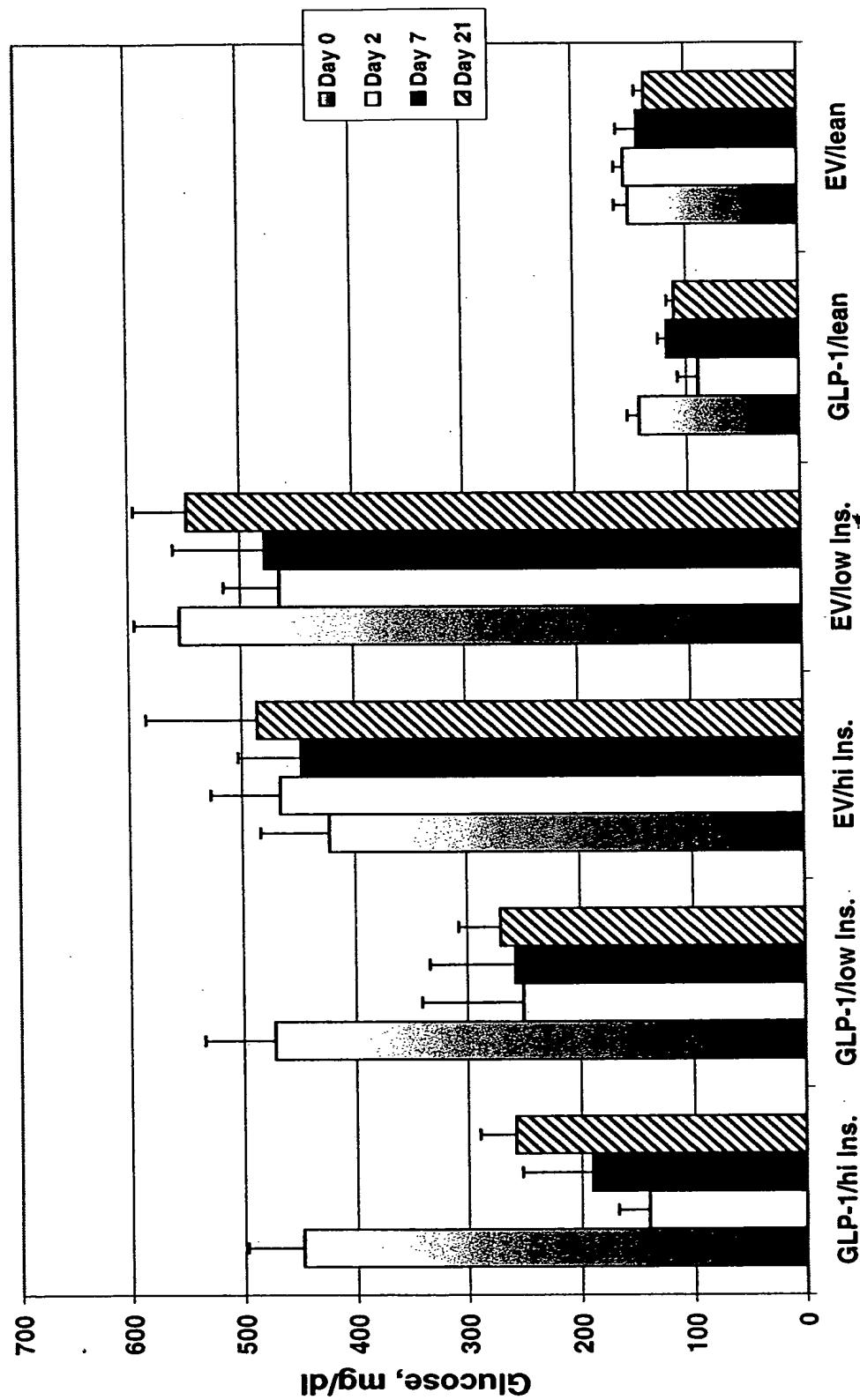


Figure 28

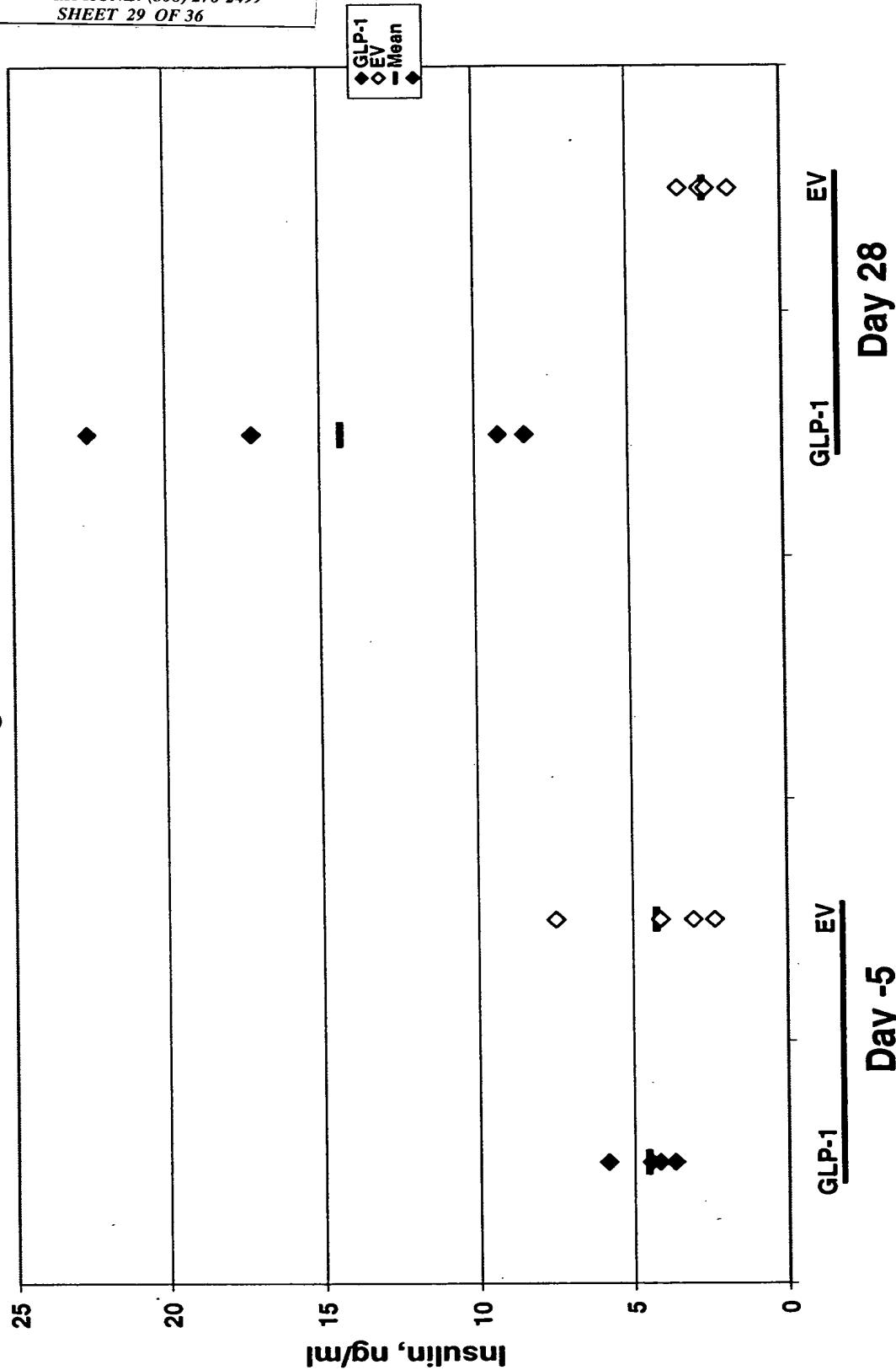


Figure 29

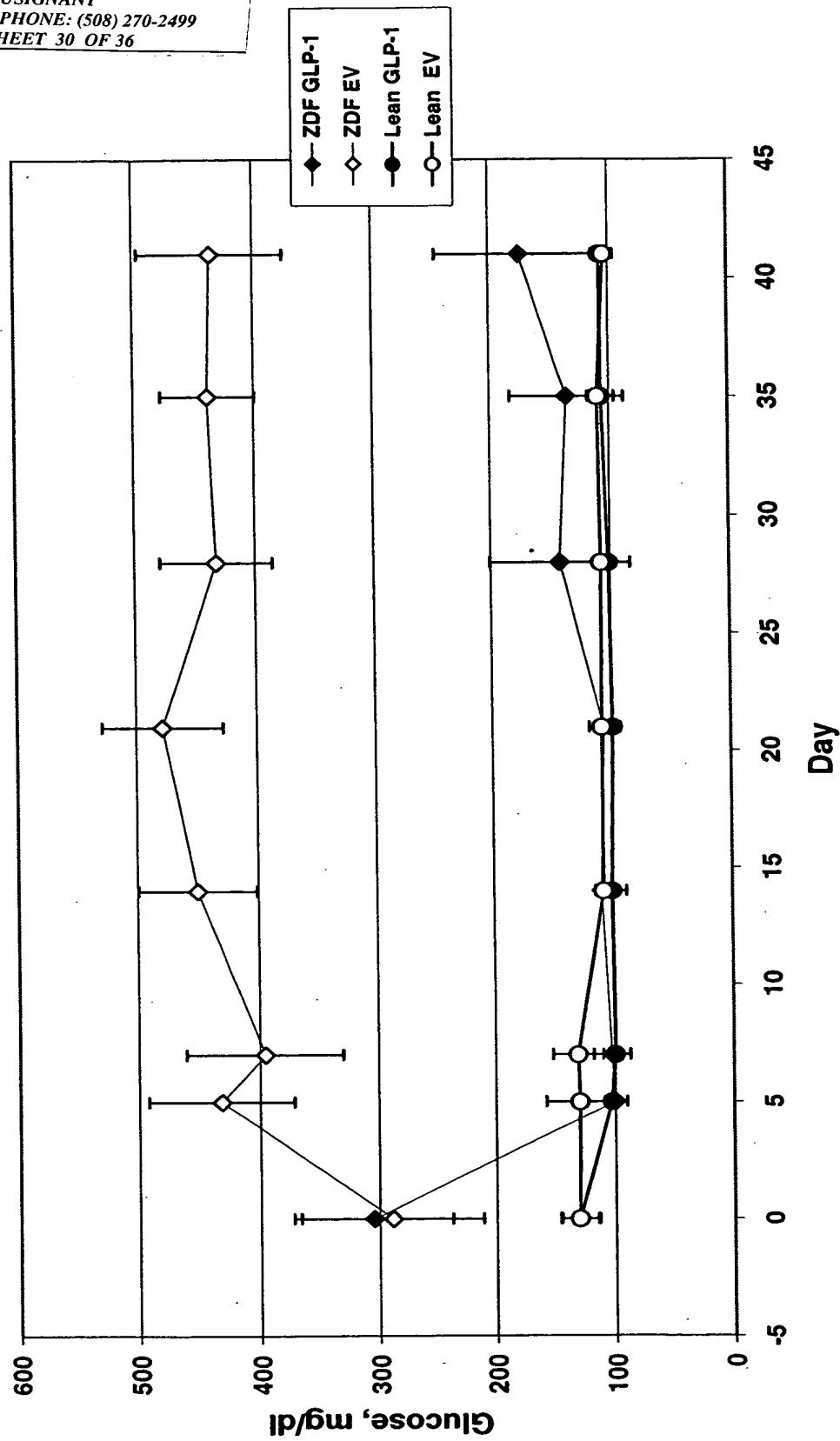


Figure 30

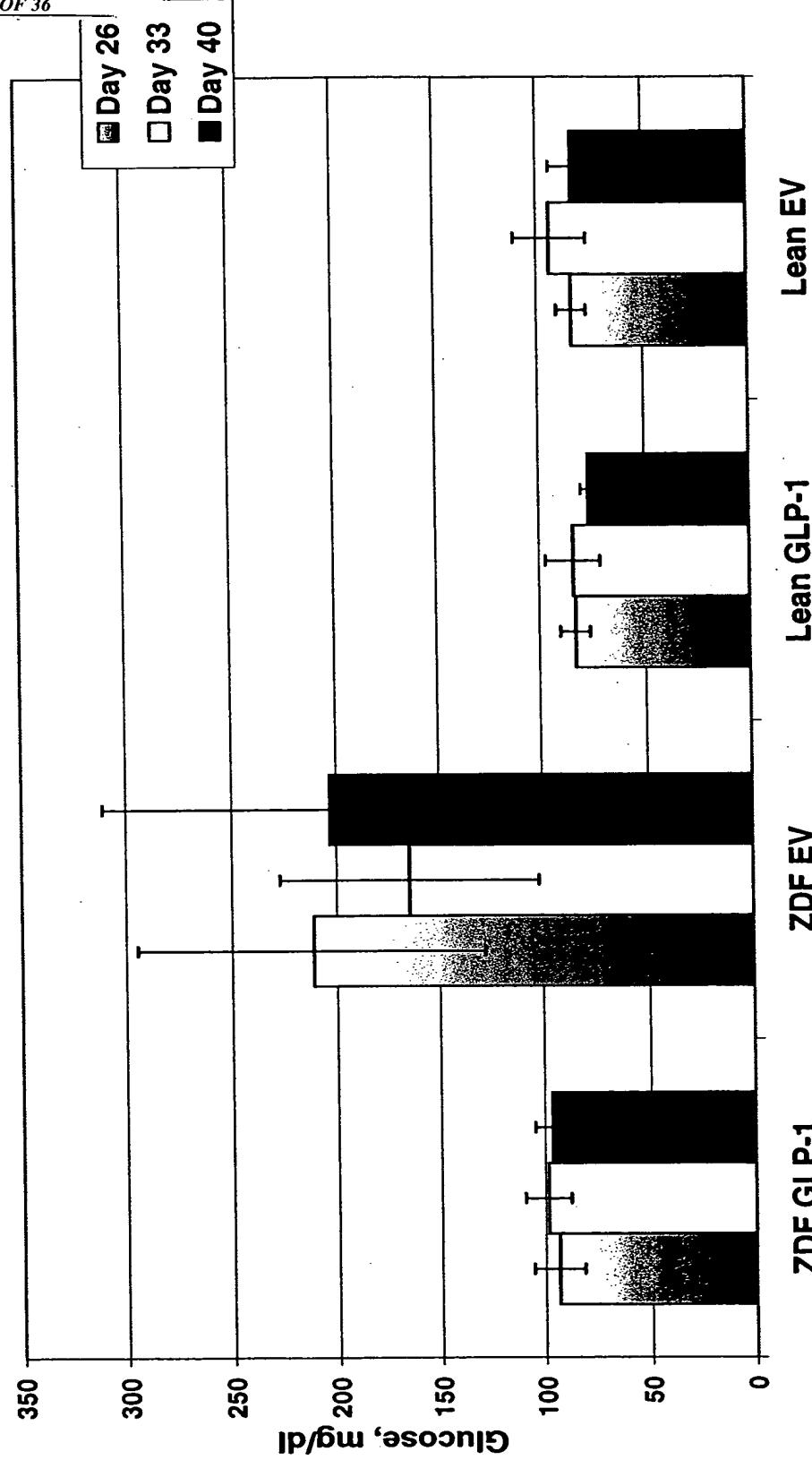
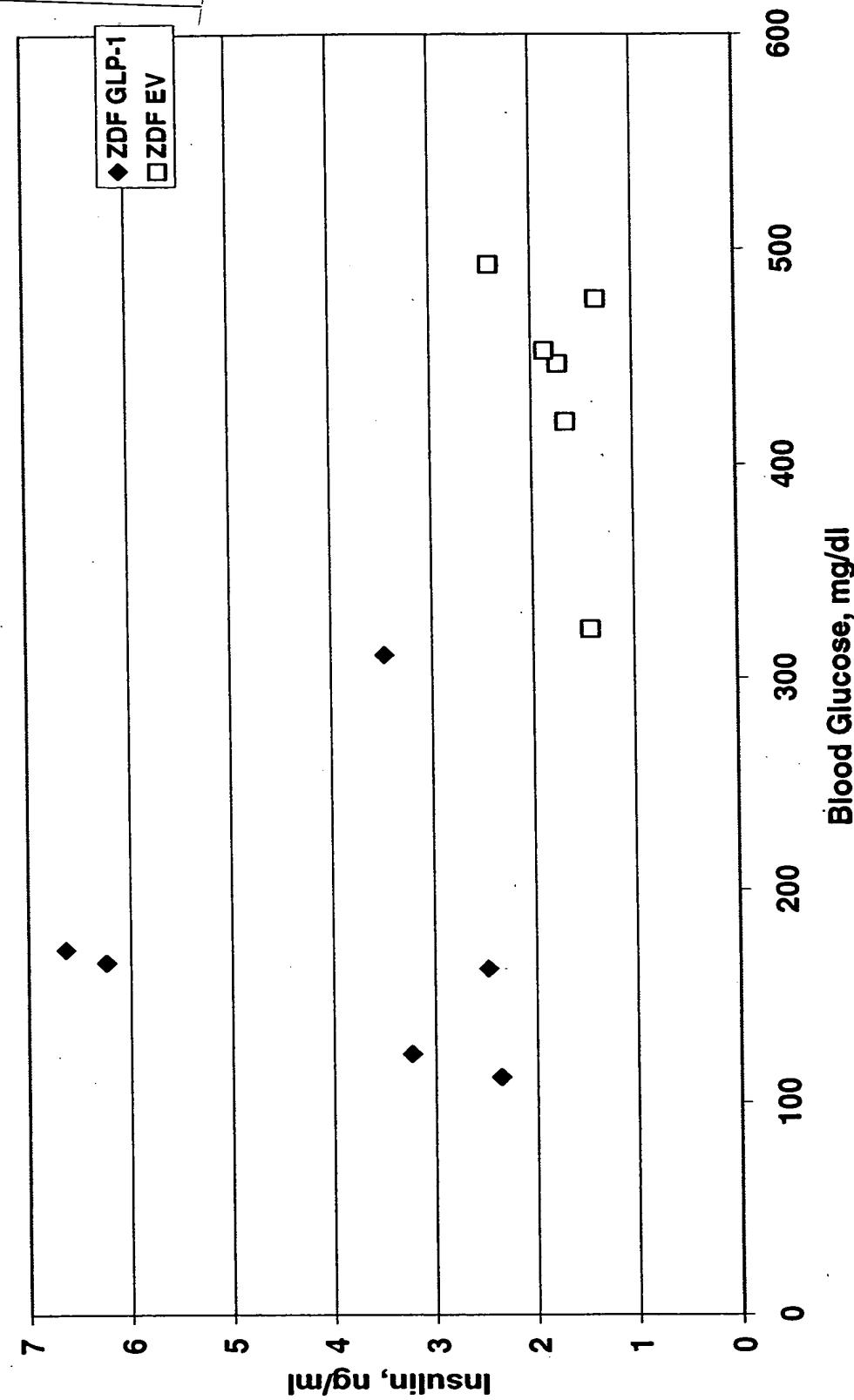


Figure 31



Day 5
 Day 28
 Day 41

Figure 32

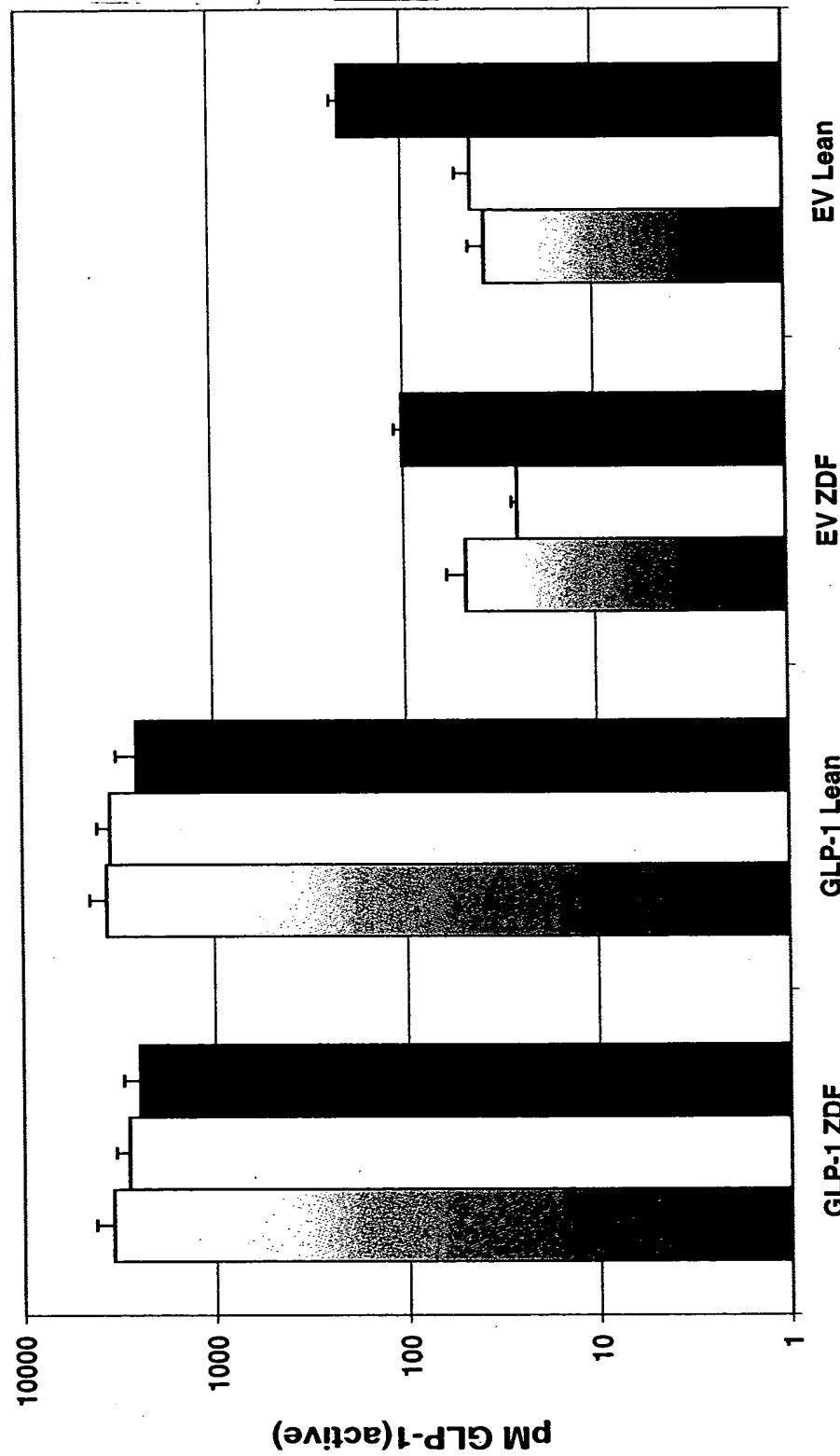


Figure 33

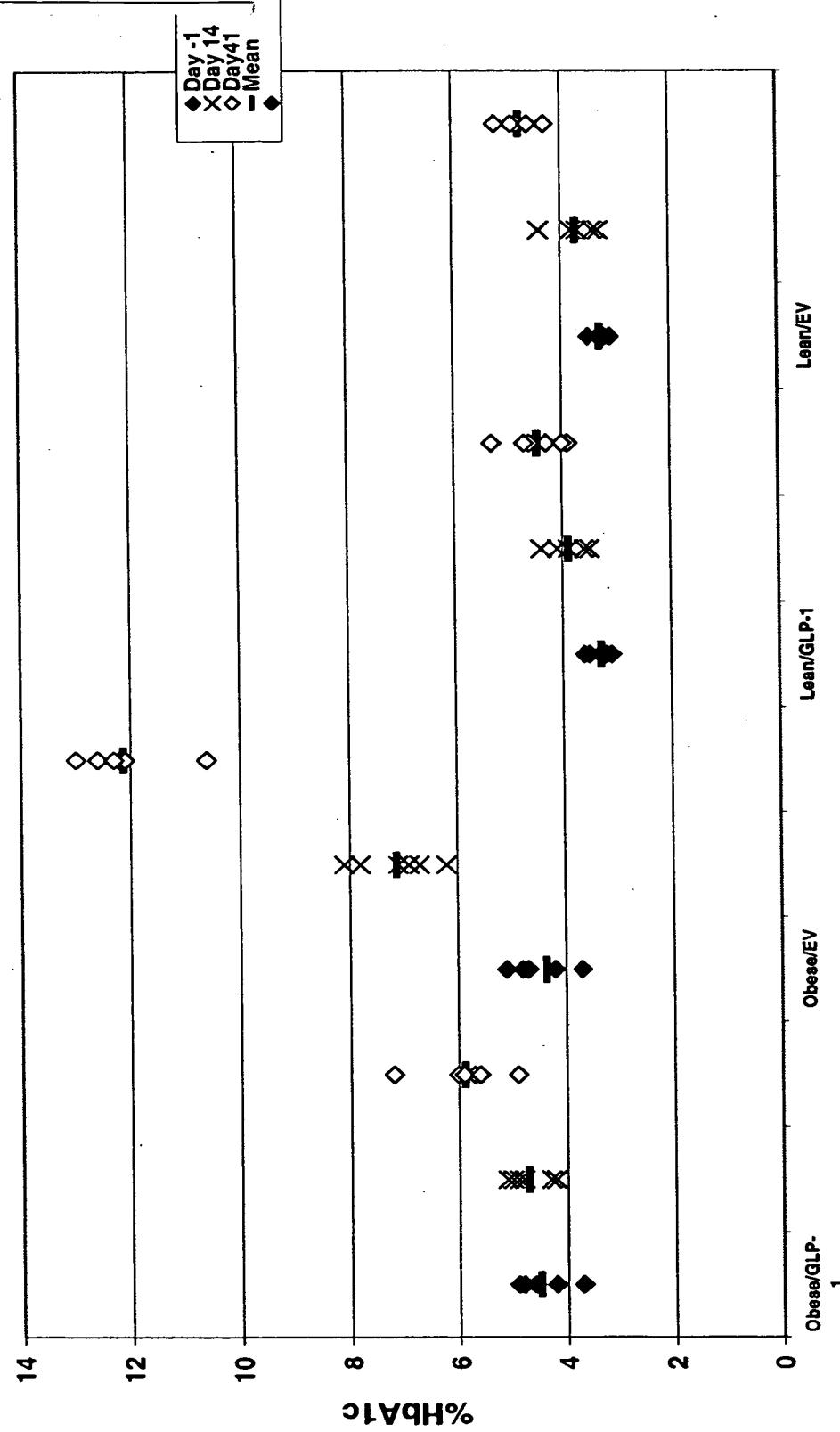
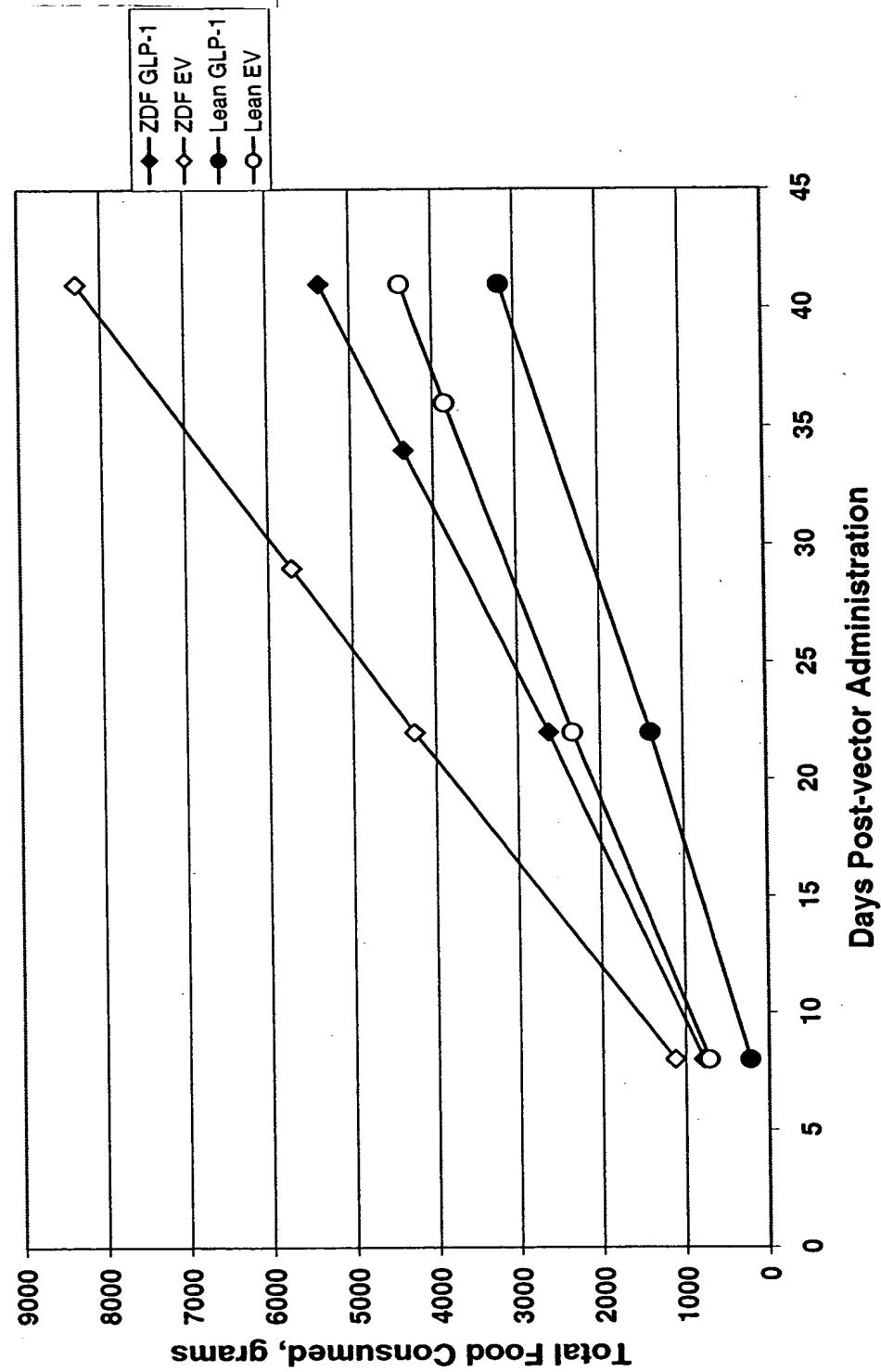


Figure 34



◆ ZDF GLP-1
◆ ZDF EV
● Lean GLP-1
○ Lean EV

Figure 35

